

Hospital Management of the Alcohol Withdrawal Syndrome



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Outline

- Epidemiology
- Definitions
- Pathophysiology
- Diagnosis
- Manifestation
- Management



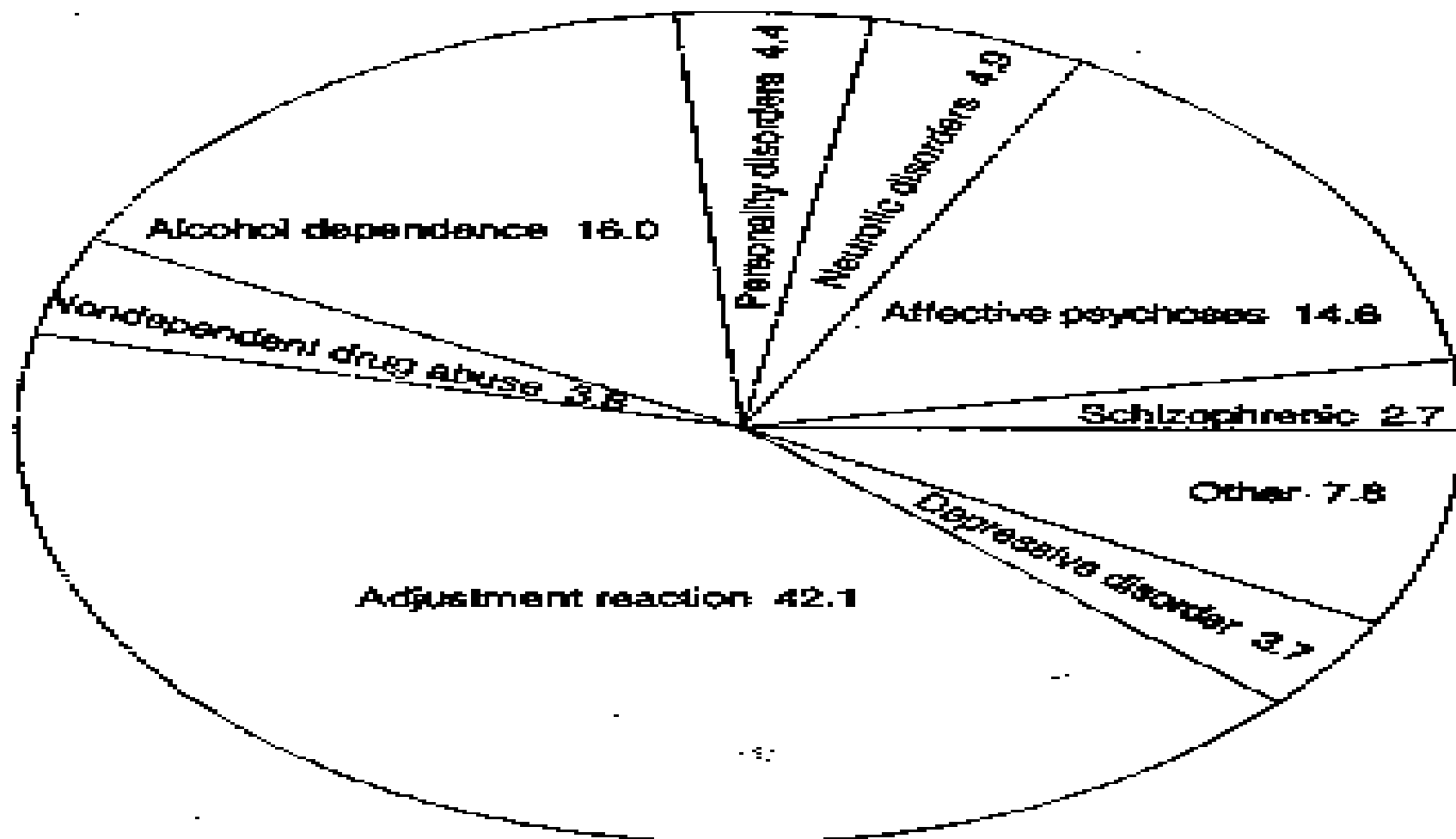


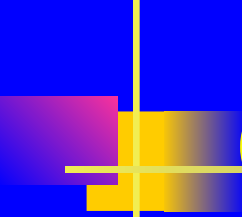
Epidemiology of Alcohol Dependence

- Lifetime prevalence is 14%
- Male predominance of 5:1
- Only 5% of alcohol dependent people are homeless

Alcohol in the Army

Figure 2. Mental health hospitalizations (%) by diagnostic criteria, active duty soldiers, 1997





DSM-IV Alcohol Withdrawal Criteria

- A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
- B. Two (or more) of the following, developing within several hours to a few days after Criterion A.
 - 1. Autonomic hyperactivity (e.g., diaphoresis or HR>100)
 - 2. Increased hand tremor
 - 3. Insomnia
 - 4. Nausea and vomiting
 - 5. Transient visual, tactile, or auditory hallucinations or illusions
 - 6. Psychomotor agitation
 - 7. Anxiety
 - 8. Grand mal seizures



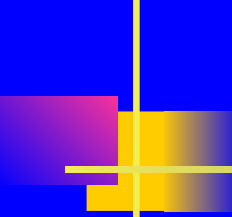
DSM-IV Alcohol Withdrawal Criteria

- C. The symptoms in Criterion B cause clinically significant distress or impairment in functioning.
- D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

Pathophysiology:

Historical Notes

- 1813: Pearson in Observations of Brain fever described alcohol withdrawal clinically calling it “acute brain fever of drunkards”
- 1813: Sutton in Tracts on delirium tremens, on peritonitis and on some other inflammatory infections named the syndrome “delirium tremens”



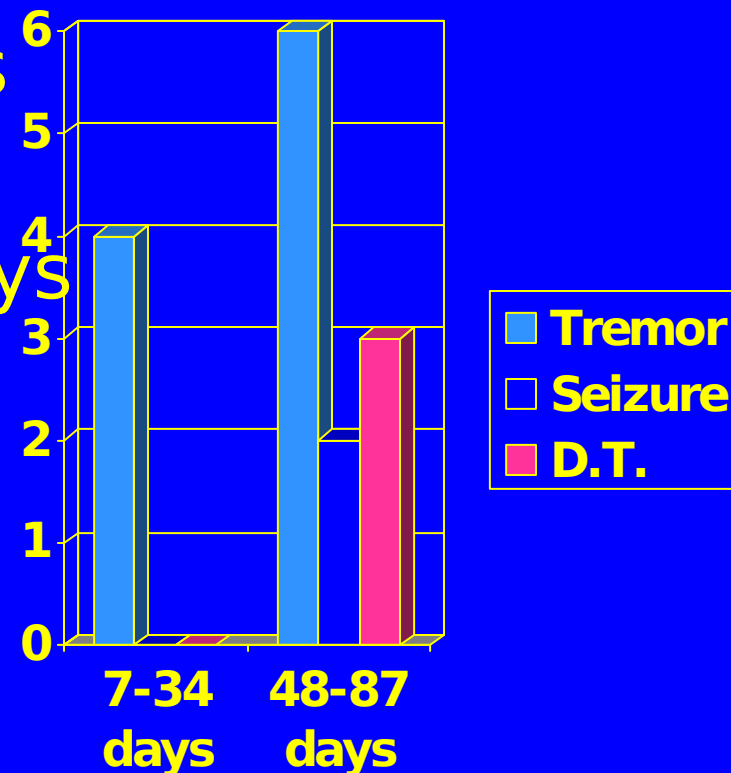
Evolution of Pathophysiology

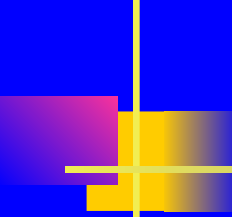
- 1953: Victor and Adams
- Studied 266 alcoholics who were hospitalized
 - 12% Seizures
 - 18% Hallucinations
 - 5% Delirium tremens
- Established that alcohol withdrawal was related to cessation

Kaim, SC et al. Treatment of the Acute Alcohol Withdrawal State: A comparison
Am J of Psych, 1969: 125: 1640-6.

Isbell's "Volunteers"

- 1955: 10 morphine addicts
- 4 men drank 266-346 ml 95% alcohol for 7 to 34 days
- 6 men drank 383-489 ml 95% alcohol for 48 to 87 days (1L whiskey)





Pathophysiology: Adaptation

- GABA (Gama aminobutyric acid A) receptor
 - Major inhibitory receptor
 - Chronic alcohol: decreases GABA A alpha 1
- NMDA (N-methyl-D-aspartate) receptor
 - Major excitatory receptor
 - Chronic alcohol: increases NMDA receptor
 - Responsible for neuronal hyperexcitability

Pathophysiology: Nutshell

- The GABA receptor is the brake
- The NMDA receptor is the accelerator
- Alcohol without accelerating



Alcohol Withdrawal Ingredients

- Alcohol dependence
- Abstinence:
 - Voluntary
 - Enforced by injury
 - Enforced by illness





Diagnosis

- History
- Physical exam
 - Stigmata of liver disease
 - Evidence of trauma
 - Evidence of infection
- Laboratory values
 - Liver associated enzymes
 - Alcohol level

Systems Altered by Alcohol

- CNS
- Gastrointestinal
- Hepatic
- Hematologic
- Cardiovascular
- Nutritional
- Metabolic

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CAGE Questionnaire

1. Have you ever felt like you should **CUT** down on your drinking?
2. Have people **ANNOYED** you by criticizing your drinking?
3. Have you ever felt bad or **GUILTY** about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**EYE OPENER**)?

Ewing, et al. Detecting alcoholism: the CAGE questionnaire. JAMA. 1984;252:



CAGE Advantages

- No difference in accuracy when use with men or women
- No difference in accuracy when use with young and old
- Short
- Fast
- Easily memorized

Kitchens, JM. Does this patient have an alcohol problem?. JAMA. 1994;272:17



Diagnostic Value of CAGE

Likelihood ratio by CAGE Score	
0	0.14
1	1.5
2	4.5
3	13.2
4	101



Withdrawal Differential Diagnosis

- Acute cocaine intoxication
- Acute amphetamine intoxication
- Sepsis
- Thyrotoxicosis
- Heat stroke
- Hypoglycemia
- Intracranial process: trauma/CVA
- Encephalitis/encephalopathy

Alcohol Withdrawal Syndrome

Stage I: Tremulousness

Stage II: Hallucinations

Stage III: Seizures

Stage IV: Delirium tremens

Not necessarily sequential





Timing of Alcohol Withdrawal

<u>Syndrome</u>	<u>Onset after last</u>
I. Tremulousness	<u>drink</u>
II. Hallucinations	6-36 hours
III. Seizures	12-48 hours
IV. Delirium	6-48 hours
Tremens	3-5 days



Stage I: Tremulousness

- Symptoms appear within 6 to 36 hours of last drink
- 13-71% of alcohol dependent patients develop withdrawal symptoms
- Caused by autonomic hyperactivity



Stage I: Tremulousness

Symptoms

- Tremor
- Anxiety
- Agitation
- Insomnia
- Diaphoresis
- Anorexia
- Nausea
- Palpitations

Signs

- Tachycardia
- Hypertension
- Hyper-reflexia
- Hyperthermia

Hall, et al. The Alcohol Withdrawal Syndrome. Lancet, 1997;349:1897-1900.

Stage II: Alcohol Hallucinations

- Occur within 12-48 hours of last drink
- 3-10 % of withdrawal develop hallucinations
- Duration is variable
- Usually visual (pink elephants)
- Occasionally auditory, tactile (formication), olfactory

Hall, et al. The Alcohol Withdrawal Syndrome. Lancet, 1997;349:1897-1900.

Erwin, et al. Delirium Tremens. Southern Medical Journal, 1998: 91: 425-32.



Stage III: Seizures “Rum Fits”

- Occur within 6 to 48 hours of last drink
- 3 to 15% of untreated patients develop seizures
- Grand mal
- Risk is increased by duration of alcohol abuse
- 40% are single episodes
- 30% of untreated patients go on to delirium tremens



Stage III: Seizures “Rum Fits”

- Alcohol is an independent risk factor for seizures
- Retrospective of 308 pts in a city hospital with new seizures
- 51-100 gm/day intake= 3 fold increase
- 101-200 gm/day intake= 8 fold increase
- 201-300 gm/day intake= 20 fold increase
 - Note 10 gm= 1 beer



Stage IV: Delirium Tremens

“In this condition the danger of death is great, and the mortality is high because delirium tremens constitutes a major ordeal for the patient’s entire system, accompanied or preceded as it may be by intoxication, disturbed nutrition, exhaustion and exposure of various types.”

Moore, et al. Delirium Tremens: A study of the cases at the Boston City Hospital
NEJM, 1939; 220: 953-6.



Stage IV: Delirium Tremens

- Begins 3 to 5 days after last drink
- Occurs in less than 5% of withdrawal patients
- Marked by disorientation and global confusion
- Mortality: 2-10%
- Death: cardiovascular, metabolic, and infections



The Days of Wine and Roses

Stage IV: Delirium Tremens

Symptoms

- Confusion
- Hallucinations
- Hyper-responsiveness

Signs

- Hypertension
- Tachycardia
- Fever

Risk Factors for Delirium Tremens

- Acute concurrent medical illness (OR of 5.1)
- More days since last drink (2 or more days)
- History of seizure or delirium tremens
- Heavier and longer drinking history
- AGE>60 increased risk for delirium and falls (OR 4.7 and 3.1 respectively)
- Elevated admission blood alcohol

Ferguson J, et al. Risk Factors for Delirium Tremens Development. J Gen Int Med 1995;10:410-14

Kraemer et al. Impact of Age on Severity, Course and Complications of Alcohol Withdrawal



Why do patients die?

“Because of the manifold complications exhibited by patients in their natural setting, it is exceedingly difficult to arrive at a clear definition of their mode of death.”

Delirium Tremens Mortality 1915-35

- Review of 2375 patients with DT 1915-1935 : overall 24% mortality (560 deaths)
- 1915: 16 patients of 31 died (52%)
- 1935: 33 patients of 243 died (14%)
 - Delirium tremens 153
 - Pneumonia 135
 - Dilatation of the heart 80
 - Brain injuries 27

Delirium Tremens

mortality

- 1950-4: 18.5% mortality
- 1954-8: 5.4% mortality
- Temp>104 = 45% mortality
- Seizures and DT= 24% mortality
- Associated with death:
 - Pneumonia
 - Liver disease
 - Hypotension
 - Trauma



Historical Management

- Poultice
- Digitalis
- Chloroform
- Alcohol
- Chloral hydrate
- Morphine
- Lumbar puncture 1915-1938
- Hydrotherapy 1930's-cold wet sheets
- 1940's non-convulsive shock therapy
- Insulin

Treatment Strategy

- Reduce symptoms
- Prevent seizures
- Prevent delirium tremens
- Prevent medical complications





Management

1. Supportive Care

2. Pharmacologic management

- Benzodiazepines
- Beta Blockers
- Clonidine
- Carbamazepine
- Magnesium
- Ethanol
- Haloperidol
- Phenytoin
- Propofol
- Gabapentin



Supportive Care

- Quiet environment
- Hydration- may have 6 L volume deficit with DT
- Electrolyte correction
- Nutrition
- Nursing care (reassurance/orientation)
- Monitor for signs/symptoms of withdrawal

Holbrook A, et al. Diagnosis and management of acute alcohol withdrawal. CMAJ 1998; 159: 155-61.
Erwin, et al. Delirium Tremens. Southern Medical Journal, 1998; 91: 425-32.



Benzodiazepines: the cornerstone

- Reduction of alcohol withdrawal symptoms in six prospective trials with:
 - Chlordiazepoxide
 - Diazepam
 - Lorazepam
- Overall reduction of seizures (7.7 per 100 treated)
- Reduction of delirium tremens (4.9 per 100 treated)
- All were equally efficacious*



Benzodiazepines

- 537 VA patients double blind control
- Randomized to:
 - Chlordiazepoxide 50 mg q6
 - Hydroxyzine 100 mg q6
 - Chlorpromazine 100 mg q6
 - Thiamine 100 mg q6
 - Or placebo

Kaim, SC et al. Treatment of the Acute Alcohol Withdrawal State: A comparison
Am J of Psych, 1969: 125: 1640-6.



Benzodiazepines

Results:	<u>Seizure</u>	<u>Delirium</u>
<u>Tremens</u>		
■ Chlordiazepoxide	1%	1%
■ Hydroxyzine	8%	4%
■ Chlorpromazine	12%	7%
■ Thiamine	4%	7%
■ Placebo	9%	8%

Kaim, SC et al. Treatment of the Acute Alcohol Withdrawal State: A comparison
Am J of Psych, 1969: 125: 1640-6.

Benzodiazepines

	Chlordiazepoxide	Diazepam	Lorazepam
Equipotent dose	25 mg	5 mg	1 mg
IM absorption	Erratic	Erratic	Complete
Duration of action	Short	Short	Intermediate
Half-life	10-30 hours	20-50 hours	10-20 hours
Metabolism	Liver	Liver	Liver
Active metabolite	N-desmethyl-Chlordiazepoxide	N-desmethyl-diazepam	None

Clinical Institute Withdrawal Assessment for Alcohol Scale-

- 10 item rating system for alcohol withdrawal severity max of 67 points.
 - 0- no symptoms
 - 1- Mild
 - 4- Moderate
 - 7- Severe
- BP and HR not found to correlate with severity of withdrawal
- Can be given in under 2 minutes

Sullivan, J.T. British Journal of Addiction, 1989; 84: 1353-7.

Clinical Institute Withdrawal Assessment for Alcohol

- ## Scale-revised (CIWA-Ar)
1. Nausea and vomiting
 2. Tremor
 3. Paroxysmal sweating
 4. Anxiety
 5. Agitation
 6. Tactile disturbances
 7. Visual disturbances
 8. Auditory disturbances
 9. Headache or fullness
 10. Orientation (0-4 points)

Fixed-dose vs. Symptom-triggered

- RCT trial of 100 VA patients in a detoxification unit
- Fixed dose: Librium q 6 hours plus q1 prn if CIWA-Ar > 8
- Symptom-triggered: Librium q1 if CIWA-Ar > 8
- Symptom-triggered advantages:
 - Treatment time was 9 hours vs 68 hours
 - 100 mg vs 425 mg total Chlordiazepoxide
 - CIWA-Ar scores in each group were identical throughout



Beta Blockers

- Reduce autonomic manifestations of withdrawal
- No effect on CNS
- Do not reduce incidence of seizures or delirium tremens
- One study showed increased delirium with propranolol



Beta Blockers

- 120 pts treated in a community hospital RCT
 - Oxazepam + Atenolol (50 to 100 mg)
 - Oxazepam + placebo
- 1 day shortened hospital stay and less benzodiazepine
 - Weakness: no one was really sick
- Recommendation: may be used in mild withdrawal
- Caveat: May mask signs of withdrawal



Clonidine

- Acts on presynaptic Alpha 2-receptors
- Suppresses sympathetic outflow
- Lessen mild to moderate symptoms
- No evidence that they reduce seizures and DT



Clonidine

- RCT of 47 patients
 - 0.2 mg clonidine
 - 50 mg chlordiazepoxide
- Clonidine lowered BP, HR, and withdrawal scores
 - No one was very sick
 - Doses were feeble- at best
- Recommendation: Mild to moderate withdrawal



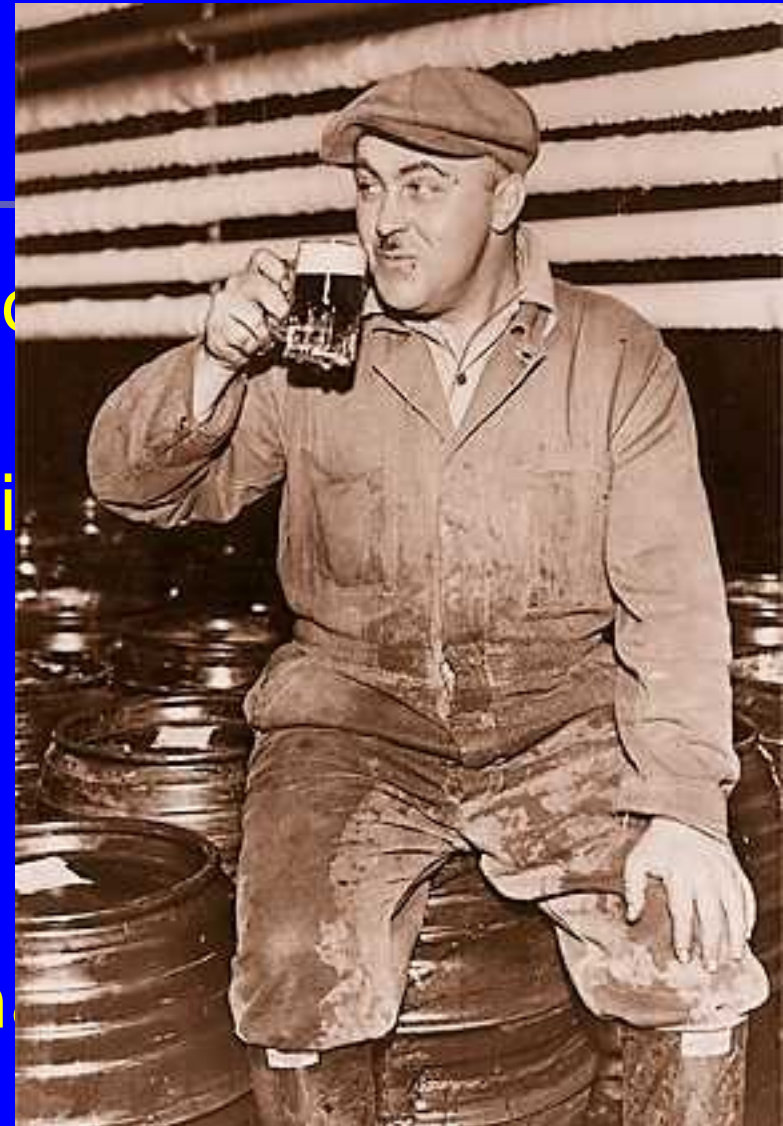
Carbamazepine

- Used as monotherapy in Europe
- May block kindling effect
- Equal to oxazepam (Serax) for mod/mild withdrawal
- No evidence on seizure/DT except for 10 day rat study:
 - 27/50 controls with seizure
 - 5/32 treated with carbamazepine
- Recommendations: No evidence.
- An Alternative? Recurrent withdrawal?

Mayo-Smith, M et al. Pharmacological Management of Alcohol Withdrawal. JAMA.
Chu NS. Carbamazapine: Prevention of alcohol withdrawal seizures. Neurology.

Ethanol

- Gastrointestinal side effects
- Metabolic derangements
- Risks of administration/ timing
- Hepatic
- Hematologic
- Neurologic
- Nutritional
- Recommendation: No. Th





Haloperidol

- Phenothiazines lower the seizure threshold (Kaim)
- Reduce agitation
- Dose 0.5-5 mg IV/IM/PO q 2-4 hours as needed
- Recommendation: May be used with severe agitation as an adjunct to benzodiazepines



Phenytoin

- Not indicated for withdrawal seizure
- RCT of 90 patients who had alcohol seizure
 - Phenytoin 1000 mg vs placebo:
 - Phenytoin: 6/45 had seizures
 - Placebo: 6/45 had seizures
- No different than placebo
- Recommendation: Consider in epilepsy or head trauma

Allredge BK, et al. Placebo-controlled trial of IV diphenylhydantoin for shortness of alcohol withdrawal seizures. Am J of Med. 1989;87: 645-8.

Thiamine

- Evidence of deficiency within 1
- 30-80% patients deficient
- Thiamine did not reduce seizures or delirium (Kaim)
- Reduces risk of Wernicke's encephalopathy
- Give 50 to 100 mg IV/IM then PO for 3 days
- Recommendation: Yes. Thiamine before



glucose.

Holbrook A, et al. Diagnosis and management of acute alcohol withdrawal. CMAJ
Kaim, SC et al. Treatment of the Acute Alcohol Withdrawal State: A comparison
Am J of Psych, 1969: 125: 1640-6.



Magnesium

- Levels are often low in 25-30% of patients
- Similar symptoms to alcohol withdrawal
- Wilson- 1984 RCT:
 - Mg showed *no difference* in withdrawal severity
- Recommendation: not indicated; treat if needed



Propofol

- Case series reports of use in refractory delirium
 - Patients requiring up to 80 mg Lorazepam/ hour
 - Used as a continuous infusion
- Advantages:
 - Rapid titration
 - Allows lower dose of benzodiazapine
- Recommendation: May consider for ICU patient refractory to benzodiazepines

McCowan, C et al. Refractory delirium tremens treated with propofol: A case series. Crit Care Med. 2000;28: 1781-4.



Gabapentin

- Two case series:
 - 6 pts treated with 400 mg for four days
 - No seizures or delirium tremens
- Withdrawal insomnia treated in 15 patients
- Recommendation: None at this time

Myrick H, et al. Gabapentin Treatment of Alcohol Withdrawal. Am J of Psych. 19
Karam-Hage M, et al. Gabapentin Treatment for Insomnia associated with Alco
Am J of Psych. 2000;157: 151.

Specific Regimens: Fielder's choice

- Monitor q4-8 by CIWA-Ar until score is 8-10 for 24 hours (or shorter interval prn)
- Symptom-triggered q hour for CIWA-Ar >8-10:
 - Chlordiazepoxide 50-100 mg
 - Diazepam 10-20 mg
 - Lorazepam 2-4 mg
 - Assess q1 hour after each dose with CIWA-Ar



Specific Regimens

- Fixed-dose schedule:
 - Chlordiazepoxide 50 mg q6 x 4 then 25 q6 x 8 doses
 - Diazepam 10 mg q6 x 4 then 5 mg q6 x 8 doses
 - Lorazepam 2 mg q6 x 4 then 1 mg q6 x 8 doses
 - Provide additional as needed with CIWA-Ar >8-10



Who goes to the ICU?

- Age over 40
- Significant cardiac disease
- Hemodynamic instability
- Marked acid-base disturbances
- Respiratory disease
- Serious infection
- Significant GI pathology
- Temp > 103 F
- Rhabdomyolysis
- History of seizure or DT
- ARF
- Benzodiazepine drip

Questions?

